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Date:

Jan. 03, 2001

By:

Leslie Lindsay

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant(s): Charles W. Bishop, et al. **Docket No.:** 17620/9316

Serial No.: **Group Art Unit:**

Filed: Herewith **Examiner:**

FOR: 24-HYDROXYVITAMIN D, ANALOGS AND USES THEREOF

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Prior to examination on the merits, please amend the subject application as follows:

IN THE SPECIFICATION

On page 1, please delete lines 2-13 and substitute therefor --This application is a continuation of U.S. Patent Application Serial Number 09/086,969, filed May, 29, 1998.--

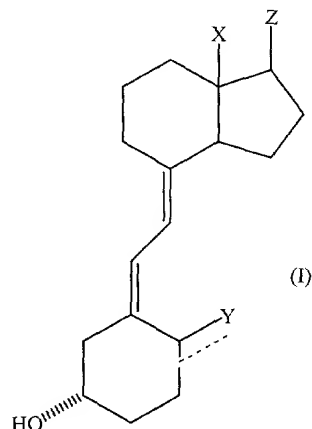
IN THE CLAIMS

Please cancel claims 1, 7-10, 12, 21-24, 26, and 27.

Please amend the claims as follows:

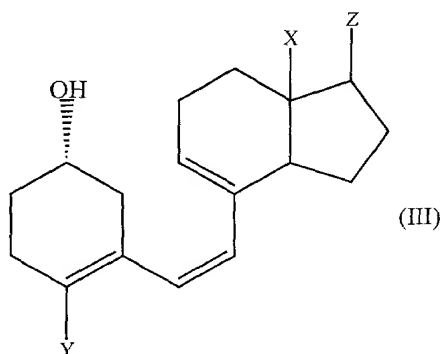
Claim 2 (Amended) A [The] method of [claim 1] achieving an effect in a patient comprising administering an effective amount of a vitamin D compound which is a 24-hydroxyvitamin D

compound wherein the effect is treating or preventing bone loss or bone mineral content, hyperparathyroidism, hyperproliferation, or modulating the immune or inflammatory response, and wherein said 24-hydroxyvitamin D is a compound of formula (I):



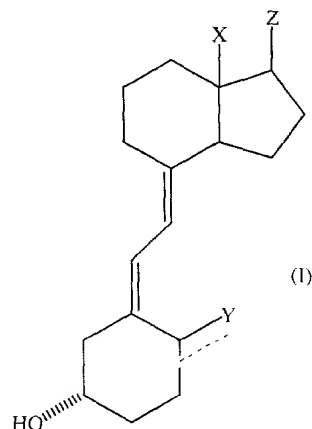
wherein Z represents a saturated or unsaturated, substituted or unsubstituted, straight-chain or branched C₄ - C₁₈ hydrocarbon group in which the C-24 or equivalent position is hydroxylated; Y is a methylene group if Y is double bonded to the A-ring or a methyl group or hydrogen if Y is single bonded; and X is hydrogen, lower alkyl or lower fluoroalkyl.

Claim 3 (Amended) [The method of claim 1] A method of achieving an effect in a patient comprising administering an effective amount of a vitamin D compound which is a 24-hydroxyprevitamin D, wherein the effect is treating or preventing bone loss or bone mineral content, hyperparathyroidism, hyperproliferation, or modulating the immune and inflammatory responses, wherein said 24-hydroxyprevitamin D is a compound of formula (III):

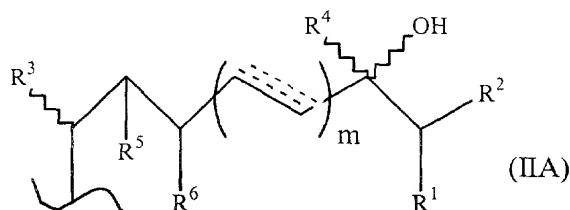


wherein Z represents a saturated or unsaturated, substituted or unsubstituted, straight-chain or branched C₄ - C₁₈ hydrocarbon group in which the C-24 or equivalent position is hydroxylated; Y is a methyl group or hydrogen; and X is hydrogen, lower alkyl or lower fluoroalkyl.

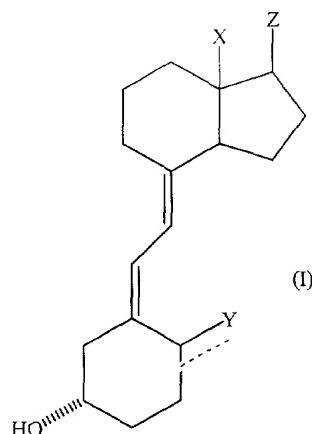
4. (Amended) The method of claim [1] 14 wherein said 24-hydroxyvitamin D is a compound of formula (I):



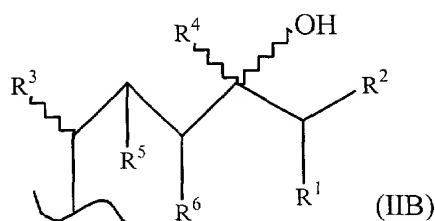
wherein Y is a methylene group if Y is double bonded to the A-ring or a methyl group or hydrogen if Y is single bonded; and X is hydrogen, lower alkyl or lower fluoroalkyl; a dotted line along the side chain represents an optional additional C-C bond and m is 0 or 1; R¹ and R² are independently lower alkyl, lower fluoroalkyl, lower alkenyl, lower fluoroalkenyl, lower cycloalkyl or, taken together with the carbon to which they are bonded, form a C₃-C₈ cyclohydrocarbon ring; R³ is hydrogen, lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; R⁴ is lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; [and] R⁵ and R⁶ are each hydrogen or taken together form a double bond between C-22 and C-23 and Z is a side chain of formula (IIA):



5. (Amended) The method of claim [1] 14 wherein said 24-hydroxyvitamin D is a compound of formula (I):



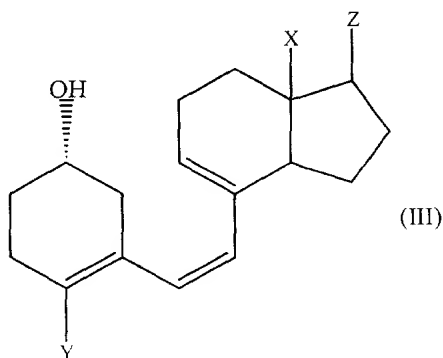
wherein Y is a methylene group if Y is double bonded to the A-ring or a methyl group or hydrogen if Y is single bonded; and X is hydrogen, lower alkyl or lower fluoroalkyl; a dotted line along the side chain represents an optional additional C-C bond and m is 0 or 1; R¹ and R² are independently lower alkyl, lower fluoroalkyl, lower alkenyl, lower fluoroalkenyl, lower cycloalkyl or, taken together with the carbon to which they are bonded, form a C₃-C₈ cyclohydrocarbon ring; R³ is hydrogen, lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; R⁴ is lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; and R⁵ and R⁶ are each hydrogen or taken together form a double bond between C-22 and C-23; and Z is a side chain of formula (IIB):



wherein R⁵ and R⁶ are each hydrogen or taken together form a double bond between C-22 and C-23, R³ is hydrogen, lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; R⁴ is lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; and R¹ and R² are independently hydrogen, lower alkyl, lower fluoroalkyl, lower alkenyl, lower fluoroalkenyl, lower cycloalkyl or taken together with the carbon to which they are bonded form a C₃-C₈ cyclocarbon ring.

11. (Amended) A method of achieving an effect in a patient comprising administering an effective amount of a vitamin D compound which is a 24-hydroxyvitamin D or a 24-hydroxyprevitamin D wherein the effect is increasing or maintaining bone mass or bone mineral content, lowering or maintaining lowered parathyroid hormone level, inhibiting hyperproliferative effects, inducing or enhancing cell differentiation [modulating immune response and] or modulating inflammatory response.

13. (Amended) [The method of claim 1] A method of achieving an effect in a patient comprising administering an effective amount of a vitamin D compound which is a 24-hydroxyprevitamin D wherein the effect is increasing or maintaining bone mass or bone mineral content, lowering or maintaining lowered parathyroid hormone level, inhibiting hyperproliferative effects, inducing or enhancing cell differentiation modulating immune response, or modulating inflammatory response, wherein said 24-hydroxyprevitamin D is a compound of formula (III):



wherein Z represents a saturated or unsaturated, substituted or unsubstituted, straight-chain or branched C₄ - C₁₈ hydrocarbon group in which the C-24 or equivalent position is hydroxylated; Y is a methyl group or hydrogen; and X is hydrogen, lower alkyl or lower fluoroalkyl.

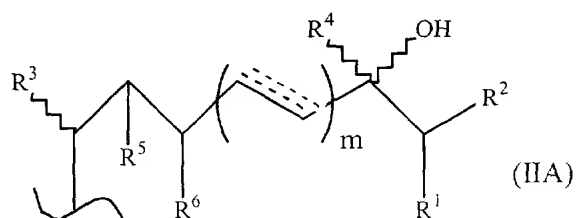
14. (Amended) A method of treating a human to alleviate the pathological effects of osteoporosis, hyperparathyroidism, psoriasis, skin cancer, breast cancer, colon cancer, prostate cancer, prostatic hyperplasia, or [and immune response imbalance and] inflammatory response [in balance] imbalance, wherein the method comprises administering to the human a vitamin D compound which is a 24-hydroxyvitamin or a 24-hydroxyprevitamin D wherein

said compound is administered to the human in an amount sufficient to increase or maintain bone mass or bone mineral content, lower or maintain lowered parathyroid hormone level, inhibit hyperproliferative effects, induce or enhance cell differentiation, [modulate immune response and] or modulate inflammatory response in the human.

17. (Amended) The method of claim [1]2, wherein said 24-hydroxyvitamin D compound is administered in a dosage of about 3.5 μg to about 1000 μg /week.

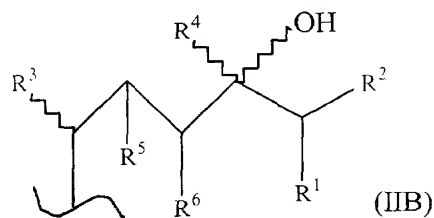
Please add the following new claims:

--28. The method of claim 3 wherein Z is a side chain of formula (IIA):



wherein a dotted line along the side chain represents an optional additional C-C bond and m is 0 or 1; R¹ and R² are independently lower alkyl, lower fluoroalkyl, lower alkenyl, lower fluoroalkenyl, lower cycloalkyl or, taken together with the carbon to which they are bonded, form a C₃-C₈ cyclohydrocarbon ring; R³ is hydrogen, lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; R⁴ is lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; and R⁵ and R⁶ are each hydrogen or taken together form a double bond between C-22 and C-23.

29. The method of claim 3 wherein Z is a side chain of formula (IIB):

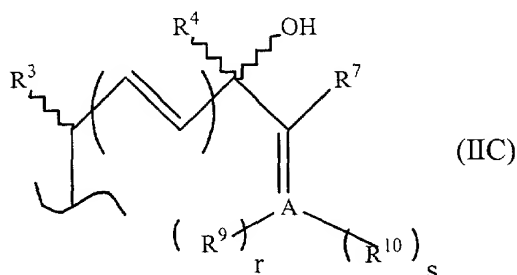


wherein R⁵ and R⁶ are each hydrogen or taken together form a double bond between C-22 and C-23, R³ is hydrogen, lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; R⁴ is lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; and

R^1 and R^2 are independently hydrogen, lower alkyl, lower fluoroalkyl, lower alkenyl, lower fluoroalkenyl, lower cycloalkyl or taken together with the carbon to which they are bonded form a C_3 - C_8 cyclocarbon ring.

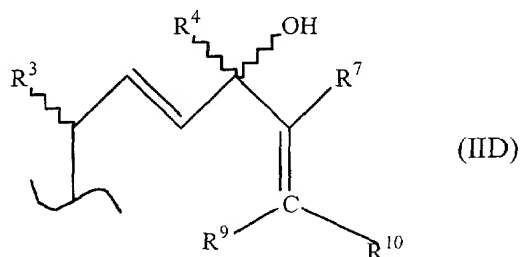
30. The method of claim 29, wherein said 24-hydroxyvitamin D is 24-hydroxyvitamin D_2 ; 24(S)-hydroxyvitamin D_2 ; 24-hydroxyvitamin D_4 ; or 24(R)-hydroxyvitamin D_4 .

31. The method of claim 3 wherein Z is a side chain of formula (IIC):



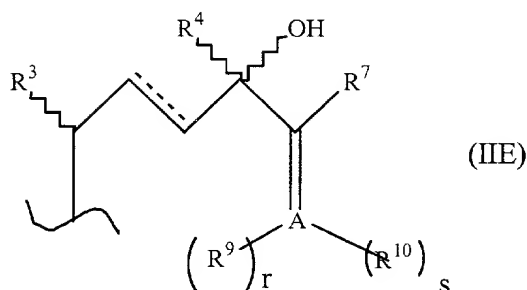
wherein n is an integer which is 1 or 2; R^3 is hydrogen, lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; R^4 and R^7 are independently lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; A is carbon, oxygen, sulfur or nitrogen; r is 1 and s is zero when A is nitrogen; r and s are 1 when A is carbon; r and s are zero when A is sulfur or oxygen; and when A is carbon, R^9 and R^{10} are independently hydrogen, lower alkyl, lower alkenyl, lower fluoroalkyl or lower fluoroalkenyl.

32. The method of claim 3 wherein Z is a side chain of formula (IID):



wherein R^3 , R^9 and R^{10} are independently hydrogen, lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; and R^4 and R^7 are independently lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl.

33. The method of claim 3 wherein Z is a side chain of formula (IIE):

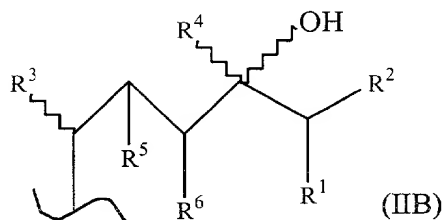


wherein a dotted line along the side chain represents an optional additional C-C bond; q is zero or an integer which is 1 or 2; R³ is hydrogen, lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; R⁴ and R⁷ are independently lower alkyl, lower fluoroalkyl, lower alkenyl or lower fluoroalkenyl; A is carbon, oxygen, sulfur or nitrogen; r is 1 and s is zero when A is nitrogen; r and s are 1 when A is carbon; r and s are zero when A is sulfur or oxygen; R⁹ and R¹⁰ are independently hydrogen, lower alkyl, lower alkenyl, lower fluoroalkyl or lower fluoroalkenyl.

34. The method of claim 33 wherein said 24-hydroxyprevitamin D compound is 24-OH-25-ene-*pre*D₂; and or 24-OH-25-oxo-*pre*D₂.

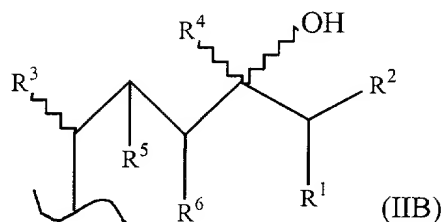
35. The method of claim 2, wherein effect is treating or preventing bone loss or bone mineral content, or hyperproliferation.

36. The composition of claim 15, wherein said 24-hydroxyvitamin D is vitamin D₂, wherein Z is a sidechain of formula (IIB):



wherein R¹ is a methyl group, and wherein R² is a methyl group.

37. The tablet of claim 25, wherein the vitamin D compound is vitamin D₂, wherein Z is a sidechain of formula (IIB):



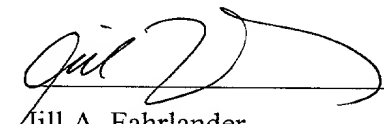
wherein X is hydrogen, wherein R¹ is a methyl group, and wherein R² is a methyl group.--

REMARKS

The Applicants believe that claims 2-6, 11, 13-20, 25, and 28- 37 are in condition for allowance, and respectfully solicit an early notice of allowance. In the event that there are any issues which can be expedited by telephone conference, the Examiner is invited to telephone the undersigned at the number indicated below.

Respectfully submitted,

Date: January 3, 2001


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